REMARKS

Independent claim 5 and claim 6 are amended by deleting the word "infectious". No new matter has been added.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 103(a)

Claims 5-16 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. patent No. 7,267,942 to Peiris *et al.* (hereinafter "Peiris II") in view of Therianos *et al.* (U.S. Patent Application Publication No. 2005/0089862; hereinafter "Therianos"). In particular, the Office Action alleges that Peiris II teaches two separate PCR reactions: (1) reverse transcription PCR ("RT-PCR") and (2) Real Time PCR, using the nucleic acid of the pathogenic agent, and the scope of the invention as claimed does not exclude amplification by RT-PCR and a second real-time PCR using the nucleic acid of the pathogenic agent. The Office Action points to column 11, lines 16-47 and column 34, lines 49 to 64 to allege that Peiris II teaches a method for detecting nucleic acid (RNA) comprising the steps of nucleic acid isolation followed by nucleic acid amplification using real time PCR.

It is alleged that although Peiris II does not teach pre-amplification before performing real-time PCR, Therianos remedies this deficiency because Therianos teaches a method for multiplex real-time PCR comprising a pre-amplification step before conducting real-time PCR, and that real-time PCR was done using the amplified product of the pre-amplification. As such, it is alleged that it would have been obvious to one of ordinary skill in the art at the time of the invention to have modified the method for detecting a nucleic acid of a pathogenic agent as taught by Peiris with the pre-amplification step as taught by Therianos.

In response, first and foremost, Applicants respectfully point out that Peiris II relies on nine provisional patent applications, and that two of these nine provisional patent applications were filed *after* the instant application's priority date. As such, Peiris II is not to be considered prior art based on subject matter of these two provisional applications. Applicants respectfully request that the examiner reconsider and withdraw the present rejection based upon the disclosures of these two provisional patent applications (provisional application numbers 60/471,200, filed May 16, 2003; and 60/468,139, filed May 5, 2003) which were filed after the instant application's priority date.

Applicants respectfully point out that, as amended, independent claim 5 is directed to a method for detection of nucleic acid of a pathogenic agent comprising the sequential steps of: (a) isolating the nucleic acid of the pathogenic agent, (b) pre-amplifying the nucleic acid of the pathogenic agent, and (c) performing Real Time PCR on the nucleic acid of the pathogenic agent that is pre-amplified in step (b). Peiris II does not teach or suggest a method for detection of nucleic acid of a pathogenic agent that comprises the sequential steps of amplifying the nucleic acid of a pathogenic agent followed by performing Real-Time PCR on the nucleic acid of the pathogenic agent. The section in Peiris II cited in the Office Action (column 11, lines 16-47) discloses the use of real-time quantitative PCR to detect the presence of hSARS virus. The amplification disclosed in Peiris II refers to the amplification that is part of the real-time PCR. In contrast, claim 5 refers to a pre-amplification step separate from the real-time PCR step.

Peiris II fails to teach or suggest such a separate pre-amplification step. Rather, Peiris II discloses a method which involves real-time PCR (*see* col. 11, lines 16-47). In Peiris II, the cDNA obtained by reverse transcription ("RT") is subject to real-time PCR reaction. Applicants

respectfully highlight that RT is a process in which RNA is reverse transcribed to cDNA using reverse transcriptase. There is no amplification before real-time PCR. Peiris II mentions "detecting the amplified product using a probe" (*see* col. 11, line 29). Real time PCR is used to amplify and simultaneously quantify a targeted DNA molecule and the amplified product is the product of the amplification during the real-time PCR. That is, in contrast to the presently claimed invention, there is no amplification (*i.e.* pre-amplification) being performed in Peiris II before the amplification that takes place in the real-time PCR process. In other words, in contrast to the present invention, there is no teaching in Peiris II of a pre-amplification step before the RT-PCR step, as presently claimed. Moreover, in contrast to Peiris II, in the present invention, after the pre-amplification step (where the nucleic acid of the pathogenic agent is pre-amplified), a separate step is performed on said nucleic acid, namely real-time PCR.

Therianos fails to remedy the deficiencies of Peiris II. Rather, Therianos discloses a method for analyzing one or more gene transcript in a given sample, disclosing compositions and methods for analyzing multiple nucleic acids using PCR. Applicants submit that there is no teaching or suggestion, either in Peiris II, Therianos or in the knowledge generally available to one of ordinary skill in the art, to modify these two references or to combine their teaching and arrive at the presently claimed invention. A person of ordinary skill in the art would not have recognized that the results of the combination were predictable, and indeed there would have been no reasonable expectation of success to arrive at the present invention by combining the teachings of Peiris II and Therianos.

Peiris II is related to a diagnostic assay for the virus causing SARS. There is nothing to suggest or at least lead or suggest a person of ordinary skill in the art to refer to a reference which teaches a method for obtaining quantitative information about the expression of different genes in a sample *e.g.* human brain cell to understand the molecular bases of human disease such as Alzheimer's Disease, a proteopathy disease in which certain proteins become structurally abnormal, and thereby disrupt the function of cells, tissues and organs of the body. Furthermore, there is no reasonable expectation of success since, for example, while Peiris II relates to a diagnostic assay for the virus causing SARS, Therianos's method discloses quantitative analyze clusters of genes or population of cells. There is no indication that the SARS can be detected and diagnosed by the method disclosed in Therianos.

The use of a pre-amplification step, as taught by the present invention, prior to performing real-time PCR provides a surprising range of benefits. In particular, as stated in paragraph [0076] of the published application:

> After the target SARS coronavirus viral RNA molecules are extracted from the biological sample, the amount of RNA molecules in the sample may not be sufficient to be detected. Therefore, a portion of the SARS coronavirus viral RNA molecule is replicated to a target nucleic acid molecule by an appropriate amplification technique, for example, polymerase chain reaction (PCR) or NASBA or RT-PCR. The target nucleic acid molecules may then be detected by suitable methods. The use of a pre-amplification step prior to RT-PCR surprisingly provides a range of benefits including greater detection levels, improved sensitivity and quicker times than provided by conventional PCR techniques alone. (emphasis added).

Indeed, based on the SARS case, a person of ordinary skill in the art can detect and diagnose an infected patient with increased sensitivity over other methods as demonstrated by the attached non-prior art publications (the two attached articles were published soon after the instant application's priority date).

The Supreme Court in the KSR decision stated that the analysis supporting a rejection for obviousness be made explicit and that rejections cannot be sustained by mere conclusory statements but, instead, there must be an articulated reason with some rational underpinning to support the legal conclusion of obviousness. The USPTO lists factors, including a) combining prior art elements according to known methods to yield predictable results, and b) simple substitution of one known element for another to obtain predictable results. Here, an ordinary skilled artisan would not have recognized that the results of combining Peiris II with Therianos were predictable, and therefore for this additional reason, the obviousness rejection based upon combining the primary Peiris II reference with Therianos is improper and should be withdrawn.

Applicants respectfully highlight that one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fritch, 972 F.2d 1260 (Fed. Cir. 1992). Using the inventor's success as evidence that one of ordinary skill in the art would have reasonably expected success represents an impermissible use of hindsight. Life Technologies, Inc. v. Clontech Laboratories, Inc. 224 F.3d 1320 (Fed. Cir. 2000). It is impermissible to engage in a hindsight reconstruction of the claimed invention by using the applicant's structure as a template and selecting elements from references to fill in the gaps. In re Gorman, 933 F.2d 892 (Fed. Cir. 1991).

MPEP 2143 recites seven rationales that may support a conclusion of obviousness: (1)

combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of known technique to improve similar devices (methods or products) in the same way; (4) applying a known technique to a known device (method or product) ready for improvement to yield predictable results; (5) "obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (6) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (7) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. With this in consideration, Applicants respectfully argue that the combination of Peiris II and Therianos does not render the instant claims as obvious, as the combination fails to support any of these rationales.

A person of ordinary skill in the art would not have recognized that the results of the combination were predictable, and indeed there would have been no reasonable expectation of success to arrive at the present invention by combining the teachings of Peiris II and Therianos. Applicants respectfully point out that a prior art reference must be considered in its entirety, *i.e.,* as a whole. *W.L. Gore & Associates, Inc. v. Garlock, Inc.,* 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied,* 469 U.S. 851 (1984). Applicants acknowledge that Pieris II teaches a diagnostic assay for the virus causing SARS, however, the mere fact that Pieris II discloses this method in the context of real-time PCR and Therianos discloses a method for determining the relative copy number of a group of nucleic acid molecules in a sample, does not teach or suggest in any way the method of the invention as presently claimed, which explicitly requires the sequential

steps of: (a) isolating the nucleic acid of the pathogenic agent, (b) pre-amplifying the nucleic acid of the pathogenic agent, and (c) performing Real Time PCR on the nucleic acid of the pathogenic agent that is pre-amplified in step (b). Moreover, there is no teaching, suggestion, or motivation in the cited references or in the prior art that would have led one of ordinary skill to modify Pieris II's real-time quantitative PCR assay for the detection of hSARS virus using reverse transcription and PCR method or to combine such teaching with Therianos's disclosure of a method for analyzing one or more gene transcripts in a given sample. Therefore, for at least this reason, Therianos cannot compensate for the deficiencies in the teachings of Peiris II.

Thus, since Peiris II in view of Therianos fail to teach or suggest the present invention as claimed in amended claim 5, the present invention would not have been obvious to one of ordinary skill. With respect to rejected claims 6-16, the Federal Circuit recently held that "[a] broader independent claim cannot be nonobvious where a dependent claim stemming from that independent claim is invalid for obviousness." (No. 2009-1076, slip op. 21-22) That is, if a dependent claim is obvious, then the parent independent claim is obvious. The logical contrapositive of this holding is that if a parent independent claim is nonobvious, then all dependent claims are nonobvious. Callaway Golf v. Acushnet, 2009-1076 (Fed. Cir. 2009).

Thus, in view of the above, withdrawal of the rejection of claims 5-16 under 35 U.S.C. §103(a) as being unpatentable over Peiris II in view of Therianos is respectfully requested.

There being no other outstanding issues, it is believed that the application is in condition for allowance, and such action is respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance,

the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

The undersigned hereby authorizes the Commissioner to charge any fee insufficiency and credit any overpayment associated with this submission to Deposit Account No. 08-1935.

Respectfully submitted,

/Shahrokh Falati/

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Encls. Yu *et al.* [N Engl J Med 350; 15, April 8, 2004]
Lau *et al.* [Biochem & Biophysical Res. Comm. 312, 1290-1296 (2003)]

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